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(54) Title: METHOD FOR MAKING 2-FLUORO-2-DEOXYGLUCOSE

(57) Abstract

A method is provided for preparing [^{18}F]2-fluoro-2-deoxyglucose with an anion exchange resin by effecting an exchange reaction between an aqueous solution of [^{18}F]fluoride containing an alkali metal carbonate or bicarbonate, such as sodium bicarbonate, and an anion, such as bicarbonate or carbonate, on the anion exchange resin followed by the displacement reaction with 1,3,4,6-tetra-O-acetyl-2-0-trifluoromethanesulfonyl-β-D-mannopyranose to form the resulting 2-fluoro-2-deoxyglucose tetraacetate. Improved yields of the [^{18}F]2-fluoro-2-deoxyglucose are obtained when the alkali bicarbonate or carbonate is used in the target water.

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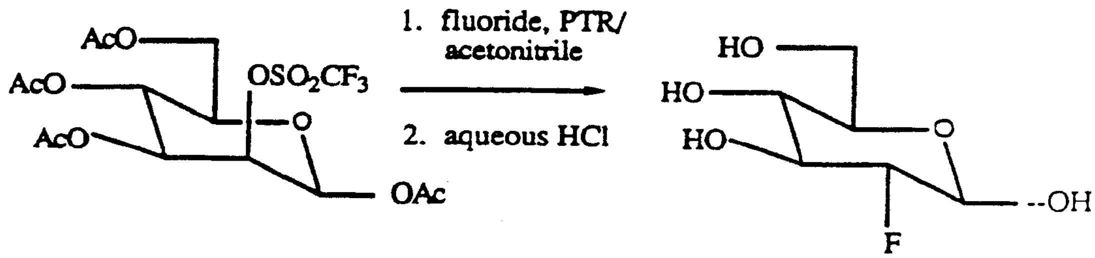
METHOD FOR MAKING 2-FLUORO-2-DEOXYGLUCOSE

Background of the Invention

The present invention relates to a method for making 2-fluoro-2-deoxy-D-glucose or [^{18}F]2FDG , utilizing an anion exchange resin. More particularly, the present invention relates to the use of an anion exchange resin to more effectively trap [^{18}F]fluoride ion, involving the treatment of the anion exchange resin having an anion, such as a carbonate or bicarbonate anion, with an aqueous solution of [^{18}F]fluoride ion target water and an alkali metal carbonate or bicarbonate salt, such as sodium bicarbonate.

Prior to the present invention, various procedures were used for making [^{18}F]2FDG, which is used as a radiopharmaceutical for Positron Emission Tomography (PET). Considerable effort has been expended in the development and refinement of such procedures. Because [^{18}F]fluoride ion has a low decay energy, (0.64 MEV), it allows the highest inherent resolution during PET measurements and has a relatively convenient half life of 109.7 min. The following equation illustrates the preferred procedure for making [^{18}F]2FDG starting tiwh a solution of 1,3,4,6-tetra-O-acetyl-2-O-trifluoromethanesulfonyl-β-D-mannopyranose or "triflate":



where Ac is acetate, and "PTR" means phase-transfer reagent.

One method of synthesizing [^{18}F]2FDG by the above procedure is shown by Hamacher et al., Journal of Nuclear Medicine, 27:235-238, (1986). Hamacher et al. employ an aminopolyether [Kryptofix 222 or K222]-potassium carbonate complex as a phase-transfer catalyst for [^{18}F]fluoride. An additional procedure for making [^{18}F]2FDG is shown by Brodack et al., Applied Radiation and Isotope, Volume 39, No. 7, pages 699-703 (1988) involving the employment of a tetrabutylammonium hydroxide as a phase-transfer catalyst in place of the aminopolyether potassium complex of Hamacher et al. Although Brodack et al. disclose that the triflate reacts with [^{18}F]fluoride ion using the tetrabutylammonium counter ion, a yield of 12-17% is reported which is significantly below the level considered acceptable for commercial robotic production of [^{18}F]2FDG.

The above procedures utilizing a phase-transfer reagent for [^{18}F]2FDG synthesis have an inherent disadvantage particularly if Kryptofix 222 is

used as the phase-transfer catalyst. Kryptofix is toxic and minor traces of the phase-transfer catalyst are often difficult to remove from the final patient dose. Elaborate methods have to be used therefore to eliminate any traces of the phase-transfer catalyst before it is used. The application of automation using such PTR is therefore rendered more difficult.

An improvement in the use of a phase-transfer catalyst for making $[^{18}F]$2FDG is shown by Johnson et al., U.S. Patent 5,169,942 which utilizes a less toxic PTR, such as a tetraalkylammonium bicarbonate. However, it has been found desirable to minimize any traces of the PTR from the final dose before intravenous use which complicates the implementation of this procedure.

As shown by S. A. Toorongian et al.,cited below, alternative methods for making $[^{18}F]$2FDG are also known which utilize an anion exchange resin to trap the $[^{18}F]$fluoride ion. However, the yields of $[^{18}F]$2FDG made by the anion exchange resin procedure have been found to be significantly less than methods employing a PTR. It would be desirable therefore to provide a procedure for improving the yield of $[^{18}F]$2FDG by using an anion exchange resin to more effectively trap the $[^{18}F]$fluoride ion and improve the yields of $[^{18}F]$2FDG.

Summary of the Invention

The present invention is based on the discovery that improved yields of $[^{18}F]$2FDG can be obtained with an anion exchange resin having a carbonate or bicarbonate anion. It has been found that if prior to direct contact between the $[^{18}F]$fluoride ion containing target water and the

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anion exchange resin, the [^{18}F]fluoride ion target water is mixed with an alkali metal carbonate or bicarbonate salt in proportions as set forth below, an enhancement in [^{18}F]2FDG yields can be obtained.

Statement of the Invention

There is provided by the present invention, a method for making [^{18}F]2-fluoro-2-deoxy-D-glucose comprising,

comprising a silanol-free organosilicon resin powder made in accordance with claim 1, a vinyl substituted methylpolysiloxane fluid, a silicon hydride siloxane fluid, an inhibitor and an effective amount of a platinum catalyst.(2) effecting the displacement of the [^{18}F]fluoride ion on the anion exchange resin of (1) with the trifluoromethanesulfonyl ester leaving group of an organic solvent solution of 1,3,4,6-tetra-O-acetyl-2-O-trifluoromethanesulfonyl-β-D-mannopyranose,

(3) treating with an aqueous hydrogen halide solution, the residue of the effluent of (2), after it has been collected from the anion exchange resin and stripped of organic solvent to effect the hydrolysis of the resulting tetraacetyl 2-fluoro-2-deoxyglucose, and

(4) recovering the resulting [^{18}F]2-fluoro-2-deoxyglucose from (3).

Among the ion exchange resins which can be employed are for example, polystyrene resin functionalized with piperidinopyridinium groups which serve to trap the [^{18}F]fluoride ion and act as a phase-transfer reagent without contaminating the mixture which is injected into the patient. The preferred anion exchange resin is the "Mulholland"

anion exchange resin which preferably has a displaceable carbonate or bicarbonate anion ionically bound to the pyridinium group.

During the initial exchange reaction between the anion exchange resin and the [^{18}F]fluoride ion, the [^{18}F]fluoride ion is introduced as an aqueous solution with an alkali metal carbonate or bicarbonate salt. Although sodium bicarbonate is preferred other alkali metal bicarbonates or carbonates can be used, such as potassium bicarbonate and sodium carbonate. The [^{18}F]fluoride ion is preferably added to an aqueous solution of the alkali metal bicarbonate within the aforedescribed concentration ranges as set forth in the Statement of The Invention.

After passage of the aqueous solution of [^{18}F]fluoride ion and alkali metal bicarbonate or carbonate through the anion exchange resin to effect exchange and more effectively trap the [^{18}F]fluoride ion on the anion exchange resin, the anionic exchange resin can be treated with an anhydrous organic solvent such as acetonitrile to remove water. The anionic exchange resin can then be heated from 70°C to 90°C prior to passage of an organic solvent solution of the "triflate", 3,4,6-tetra-O-acetyl-2-O-trifluoromethanesulfonyl-β-D-mannopyranose to effect exchange between the triflate leaving group and the [^{18}F]fluoride ion. The anionic exchange resin can then be rinsed with additional organic solvent.

The effluent from the anionic exchange resin can be stripped of organic solvent under a stream of nitrogen or helium under reduced pressure. The residue can then be treated with an aqueous acid halide, such as an 2 N HCl solution and refluxed for a sufficient period of time, such as 10 to 20 minutes to effect the hydrolysis of the [^{18}F]2FDG tetraacetate.

The resulting solution can then be passed througn ion retardation resin, reverse phase silica gel and an alumina sep-pak into a collection vial. Radioactivity in the collection vial can be measured and the purity assessed by TLC.

In order that those skilled in the art will be better able to practice the present invention, the following example is given by way of illustration and not by way of limitation. All parts are by weight.

Example

There was added 0.5 to 1.5 μmol of sodium bicarbonate and 10 to 500 μl of deionized water to 1.0 to 1.5 ml of water which was obtained from a cyclotron target containing 0.5 to 10 mCi of [^{18}F]fluoride in a receiver vessel. The resulting solution was passed through a column having 10-20 mg of a 2% crosslinked anion exchange resin, specifically (Mulholland) anion exchange resin in the carbonate form, (shown by S.A.Toorongian et al; NuCl.Med.Biol.17:273-279 (1990)Int. J. Radiat. Appl. Instrum. Part B). One ml of dry acetonitrile was then passed through the resin to remove water. The anion exchange resin was then heated to 80 to 90°C and a solution of 1,3,4,6-tetra-O-acetyl-2-O-trifluoromethanesulfonyl-β-D-mannopyranose (triflate) in acetonitrile where the solution contained 30 mg of the (triflate) in 0.75 ml of acetonitrile, was pushed through the resin column to effect displacement. The column was then rinsed with 0.5 ml of acetonitrile. Effluent was collected in a plastic vessel and the acetonitrile was removed in a stream of nitrogen with heating under reduced pressure. The resulting residue was then treated with 2 ml of 2 N hydrochloric acid and refluxed for 15 minutes to effect hydrolysis of the [^{18}F]2FDG

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tetraacetate. The resulting solution was passed through an ion retardation resin (Biorad AG-11A8), reverse phase C18 silica gel (Supelco SPE), (Waters) and alumina sep pak (Waters) to a collection vial. The radioactivity in the collection vial was measured and the purity assessed by TLC. The following results were obtained where the reported yields are not decay corrected, and n is the number of runs:

Table 1

Yields of [^{18}F]2FDG

0.5 µmol $NaHCO_3$ in Target Water	Yield	95% confidence level	n
Yes	39.5%	4.4%	7
No	35.7%	2.3%	21

The above procedure was repeated except that the yield of the [^{18}F]2FDG tetraacetate was measured. There was used 0.3 µmol of sodium bicarbonate solution in the target water and the column was heated at 80°C to 90°C. The following results were obtained where the yields are corrected for decay:

Table 2

Yields of [^{18}F]2FDG Tetraacetate

0.3 µmol $NaHCO_3$ In Target Water	Column Temp (°)	Yield	95% confidence level	n
Yes	90°C	69.6%	4.7%	12
No	90°C	56.0%	11.7%	4
Yes	80°C	69.4/%	2.5%	5
No	80°C	53.3%	9.0%	6

As shown by the results in Tables 1 and 2, significantly improved yields of [^{18}F]2FDG and the corresponding tetraacetate were obtained when $NaHCO_3$ was used in the target water in accordance with the practice of the present invention.

Although the above example is directed to only a few of the very many variables which can be used in the practice of the method of the present invention, it should be understood that the present invention is directed to the use of a much broader variety of alkali metal carbonates or bicarbonates as well as conditions shown in the description preceding this example.

What is claimed is:

1. A method for making 2-fluoro-2-deoxy-D-glucose comprising,

1) effecting an anion exchange reaction between [^{18}F]fluoride ion and an anion ionically bound to an anionic exchange resin, where the [^{18}F]fluoride ion is employed as an aqueous solution of [^{18}F]fluoride ion and 10 to 60 nmol of an alkali metal carbonate, or bicarbonate salt, per μmol of anionic sites on the resin,

(2) effecting the displacement of the [^{18}F]fluoride ion on the anion exchange resin of (1) with the trifluoromethanesulfonyl ester leaving group of an organic solvent solution of 1,3,4,6-tetra-O-acetyl-2-O-trifluoromethanesulfonyl-β-D-mannopyranose,

(3) treating with an aqueous hydrogen halide solution, the residue of the effluent of (2), after it has been collected from the anion exchange resin and stripped of organic solvent to effect the hydrolysis of the resulting tetraacetyl 2-fluoro-2-deoxyglucose, and

(4) recovering the resulting [^{18}F]2-fluoro-2-deoxyglucose from (3).

2. A method in accordance with claim 1, where the anion on the anion exchange resin is a carbonate or bicarbonate anion.

3. A method in accordance with claim 1, where the anion exchange resin is a polystyrene resin functionalized with piperidinopyridinium groups.

4. A method in accordance with claim 1, where the alkali metal bicarbonate used in combination with [^{18}F]fluoride ion is sodium bicarbonate.

5. A method in accordance with claim 1, where the organic solvent is acetonitrile.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/02366

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :C07H 1/00
US CL :536/18.4, 18.5, 18.6
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/18.4, 18.5, 18.6

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	Nucl. Med. Biology, volume 17, No. 3, issued 1990 Steven A. Toorongian et al. "Routine Production of 2-Deoxy-2-[18F] Fluoro-D-glucose by Direct Nucleophilic Exchange on a Quarternary 4-Aminopyridinium Resin," pages 273-279, see page 274, column 1, line 27 through column 2, line 43.	1-3 and 5 ---------------- 4

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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